Postmenopausal Pellet vs. FDA approved Hormonal Therapy: An Assessment of Serum Estradiol and Testosterone Levels

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BACKGROUND

- Hormone therapy (HT) refers to the use of either synthetic or animal derived estrogen or combination estrogen /progesterone for prevention or treatment of diseases.
- It was approved by FDA to treat menopausal symptoms.
- It was widely used through 1990s, but use fell dramatically after the publication of the initial safety results from the Women's Health Initiative (WHI) trials in 2002.
- A gap between the need of treatment for menopausal symptoms and public concern over the safety of HT explained the fact that many women seek a “safer” alternative treatment options – custom-compounded bioidentical hormone therapy (CBHT).

- CBHT has been marketed as more natural and safer, although it has not been FDA-approved and regulated, the scientific evidence supporting those claims is lacking.
- Several marketed compounded CBH products:

  Tri-estrogen (tri-est): mixture of 80% estriol, 10% estrone, and 10% estradiol

  Bi-estrogen (bi-est): mixture of estriol and estradiol in a ratio of 8:1 or 9:1

  Testosterone and DHEA
- Testosterone may be the primary reason why women want to stick to CBHT.

- There is no proof that CBHT have fewer side effects or are more effective than FDA-approved products. In fact, many FDA-approved products are bioidentical.
- Pellet Hormone therapy (PHT) is a percutaneous form of CBHT with effects lasting 3-6 months.
- Our team have presented safety results of PHT in the 2017 & 2018 NAMS meetings, which showed a significantly higher rates of side effects (mood swing, anxiety, breast tenderness, change in hair pattern, acne, weight gain), AUB and subsequent hysterectomy in PHT. This was despite progesterone supplementation.

OBJECTIVE

- Due to lack of regulation and monitoring, possible overdosage or underdosage, and variable bioavailability of compounded hormones, laboratory monitoring become critical for women on long-term CBHT.
- The objective of the study was to assess the serum estradiol (E2) and total testosterone (T) levels in postmenopausal women treated with PHT and FHT.

METHODS

- Retrospective cohort study (PHT vs FHT)
- 539 postmenopausal women with menopausal symptoms identified from Reading Hospital EMR system
  - 384 women on PHT (estradiol [E2, 6-37.5mg] and/or testosterone [T,12-137.5 mg] pellets)
  - 155 women on FHT
- Serum E2 and T levels, treatment duration, and the number of lab follow-up were extracted from medical records.

RESULTS

- Women on PHT were significantly younger than those in FHT, with mean age (SD) of 51.04 (7.52) and 60.61 (9.56) years ($p<.001$)
- Women on PHT had significantly longer treatment duration in years than those on FHT (mean [SD]: 3.92 [2.34] vs. 3.33[4.64], $p<0.0001$).
- Of 384 women on PHT, 373 (97.1%) had serum E2 and T monitored at least once, with mean (SD) total number of E2 and T follow-up of 6.81 (4.57) and 4.98 (3.52), respectively.
- Of 155 women on FHT, 33 (21.2%) had serum E2 and T monitored at least once, with mean (SD) number of E2 and T follow-up of 0.39 (0.86) and 0.14 (0.49), respectively.

- Mean (SD, Min-Max) highest E2 (pg/mL) was significantly higher in PHT group than those in FHT (237.70 [168.55, 10-1111] vs. 93.45 [130.77, 5.5-465.8], P<0.00001).
- Mean (SD, Min-Max) highest T (ng/dL) was significantly higher in PHT group than those in FHT (192.84 [82.31, 4.3-475] vs. 15.59 [19.52, 0.2-70], P<0.00001).
- Of those on PHT, 4 women had E2 level > 1000 pg/mL and 9 women with T level > 400 ng/dL.

TABLE 1. COMPARISON OF SERUM E2 AND T LEVEL BETWEEN PHT AND FHT COHORTS

	Mean (SD)		P value*	Postmenopausal Reference Range
	PHT (n=384)	FHT (n=155)		
HT Duration (years)	3.92 (2.34)	3.33 (4.64)	**<0.0001**	
Lowest E2 (pg/mL)	59.97 (42.07)	40.93 (60.40)	**<0.00001**	<6.0 - 54.7 pg/mL
Highest E2 (pg/mL)	237.70 (168.55)	93.45 (130.77)	**<0.00001**	
Lowest T (ng/dL)	66.91 (50.4)	12.37 (21.18)	**<0.00001**	3 - 41 ng/dL
Highest T (ng/dL)	192.84 (82.31)	15.59 (19.52)	**<0.00001**	
# of Lab F/U for E2	6.81 (4.57)	0.39 (0.86)	**<0.00001**	16 over 4 years of PHT
# of Lab F/U for T	4.98 (3.52)	0.14 (0.49)	**<0.00001**	

* P values were calculated by Mann Whitney U test based on mean (SD) comparison.

TABLE 2. COMPARISON OF SIDE EFFECT FREQUENCY BETWEEN PHT AND FHT COHORTS

Side Effects	PHT (n=384)	FHT (n=155)	P-value
Overall	193 (50.3%)	23 (14.8%)	**<0.00001***
Mood swing	37 (9.6%)	4 (2.6%)	**0.0052***
Anxiety	78 (20.3%)	19 (12.3%)	**0.028***
Breast tenderness	40 (10.4%)	5 (3.2%)	**0.0063***
Hair pattern change	52 (13.5%)	5 (3.2%)	**<0.001***
Acne	34 (8.9%)	2 (1.3%)	**0.0015***
Weight gain	136 (35.4%)	8 (5.1%)	**<0.00001***
Hypertension†	57 (16.9%)	25 (20%)	0.43
Dyslipidemia†	42 (12.3%)	29 (25%)	**0.0011***
Diabetes mellitus†	14 (3.7%)	9 (6.2%)	0.22

†Newly onset cases after HT; prior history not included

DISCUSSION

- Recent prescription rates for custom-compounded pellet HT now approach those of FDA-approved hormone prescriptions
- 28-68% of women on HRT are on pellet HT, 86% of women are unaware that it is not FDA approved
- Individualized options for hormone therapy are available to women using FDA-approved options with many dosages/delivery options available
- CBHT may be an option for patients who cannot tolerate other forms of FDA-approved medication (ie. allergies)

DISCUSSION

- Compared to women on FHT, women on PHT had a significantly higher levels of peak E2 and T during treatment
- Most women have E2 and T tested when on PHT but frequency of lab monitoring was lower than expected
- Women on PHT had significantly more side effects overall when compared to women on FHT

LIMITATIONS OF THE STUDY

- Short duration
- Retrospective nature of the study
- Single site
- Unable to assess serum E2 and T responses to dose adjustment
- Unable to assess symptoms improvement after dose adjustment
- Unable to accurately correlate abnormal lab with side effects

CONCLUSION

- When compared with women on FDA-HT, women on PHT had a significantly higher and abnormal level of peak E2 and T during the treatment.
- Although most women had E2 and T tested when they were on PHT, the frequency of laboratory monitoring was still lower than expected.
- Future prospective studies are needed to help develop a clinical guideline for safety monitoring in women on CBHT.

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